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I, JULIE BILLINGSLEY, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2002950657 for a patent by ALCHEMIA PTY LTD as filed on 08 August 2002.

WITNESS my hand this
Twenty-third day of October 2003

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DERIVATIVES OF MONOSACCHARIDES FOR DRUG DISCOVERY

FIELD OF THE INVENTION

This invention relates to new compounds and methods for the preparation of combinatorial libraries of potentially biologically active compounds based on natural and unnatural monosaccharides. These compounds are functionalized, with a view to varying lipid solubility, size, function and other properties, with the particular aim of discovering novel drug or drug-like compounds, or compounds with useful properties. The invention provides intermediates, processes and synthetic strategies for the solution or solid phase synthesis of monosaccharides, variously functionalised about the sugar ring, including the addition of aromaticity and charge, the addition of pharmacophoric groups and the placement of amino acid and peptide side chain units or isosteres thereof.

BACKGROUND OF THE INVENTION

In the field of drug discovery there is a constant need for novel scaffolds that enable the rational design of potentially bioactive molecules. Carbohydrates have recently come under scrutiny as offering a source of scaffolds that allow for a high degree of substitution, and offer access to both functional and structural diversity. The nature of monosaccharide molecules is such that there are numerous different stereoisomers available that can provide access to a greater degree of molecular space than do the scaffolds presently employed in drug discovery.

Carbohydrate monomers predominantly contain hydroxyl groups but also may contain other functionalities such as an amino and/or carboxylate function. In essence, the concepts involved in drug discovery through carbohydrate based molecular and structural diversity, are twofold: (1) The primary concept involves the exploitation of the high functional density found around the carbohydrate ring to display several different moieties of biological relevance. There is a dual significance to this substitution in that (i) the substituents relative position around the ring may be varied in relation to each other and, (ii) each individual moiety may be substituted for a class of such moieties and therefore themselves may be varied (by example: an arginine

mimetic may be substituted at position 1, 2, 3, 4 or 5 around a ring in relation to other peptidomimetics, by the same token the arginine mimetic may represent a class of different arginine bioisosteres which may all be similarly substituted). (2) The second concept involves exploiting the structural diversity inherent in carbohydrate isomers. Each of the substituents around a carbohydrate ring may theoretically be presented in either an axial or equatorial configuration allowing access to hugely diverse molecular spaces. Many monosaccharides are naturally occuring, which aside from being useful in their own right, present themselves as cheap starting materials to access more exotic configurations.

There are other factors that promote carbohydrates as useful building blocks for drug discovery, for example the relative positions of the functional groups on the sugar rings are conveniently spaced such that they can effectively enable mimicry of (for example), peptide motifs such as peptidic turns and loops, as well as cyclic peptides.

The major difficulty encountered in attempts to employ monosaccharides as scaffolds, is associated with monosaccharide chemistry. In the past carbohydrate chemistry was considered arduous, protracted and not cost effective. Particularly, the degree of orthogonal protection group chemistry required to allow free access to any one of a monosaccharide's functional groups (usually five) was deemed too high to ever be effected in a commercially viable manner. As a corollary, the more easily effected peptide synthesis only requires a maximum three orthogonal protecting groups, additionally the conditions required for peptide synthesis are often milder, thus peptide synthesis has so far been able to be effected more easily than carbohydrate synthesis. Fortunately, recent developments in synthetic carbohydrate chemistry have begun to allow regular access to carbohydrates as molecular scaffolds. In a recent patent application (PCT AU00/00025) we disclosed a range of orthogonally protected building blocks suitable for oligosaccharide synthesis. The building blocks presented in this application are also suitable for use as intermediates in the synthesis of compounds of the present invention, and represent compounds and methods which define the state of the art.

To date there have been a number of disclosures relating to inventions wherein carbohydrates templates have been employed as scaffolds. Early work by Hirschmann and co workers disclose the preparation of a range of compounds in which a glucose scaffold is "decorated" with functional moeties in an attempt to develop RGD inhibitors (PCT/US94/012233). This work represents the first real attempts to prepare carbohydrate derivatives for drug discovery purposes. The compounds of Hirschmann's publications are all prepared in a systematic stepwise fashion and the methods disclosed by Hirschmann et. al. are not amenable to the production of libraries of compounds. The compounds of the current invention are all chemically and biologically stable ethers, amides and ureas and are prepared by methods which are not obvious over the work of Hirschmann.

Similarly, Alchemia Pty Ltd has disclosed in PCT/AU01/01307 building blocks, methods of syntheses, and final products relating to the employment of monosaccharide compounds as drug like molecules. The compounds of PCT/AU01/01307 are specifically directed at inhibitors of the muramyl cascade of enzymes and are hereby excluded from specification by the incorporation of this reference. A number of other publications relating to muramyl type compounds have appeared in the literature. Liu et. al. (Biorg. Med Chem Lett., 10, 2000, 1361-1363) present a series of compounds containing a benzyl glycoside at the anomeric position, an acetate at C-2 and a peptide homologated lactate at C-3 of a glucosamine scaffold. These compounds and those disclosed by Xiao (Peptides: Biol and Chem., Proc. 5th Int. Chinese Peptide Symp., 1998 CA: 134:178795) represent compounds and methods which help define the art of carbohydrate chemistry but are not directly relevant to the current invention.

Sabesan (US patent 5,220,008) discloses a series of higher oligosaccharides as inhibitors on influenza. Within the claims of this patent, a partially protected monosaccharide (structure IV) is also disclosed. The compounds of this structure are protected monosaccharides for oligosaccharide synthesis which are known in the current art and do not represent compounds

for drug discovery. Furthermore, the compounds of this structure are not amenable to a combinatorial synthesis as disclosed in the current invention.

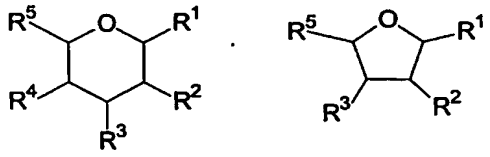
Researchers from the group of Kunz have disclosed related compounds achieved *via* alternated methodologies in a specification WO 99/07718 wherein 2-deoxy 2-amino sugars are employed as scaffolds for drug discovery. The disclosures relate specifically to the use of glucose, galactose and mannose as scaffolds and the methods disclosed are not generally applicable to other monosaccharide scaffolds. The compounds are all O glycosides which are further limited by a narrow range of unsubstituted substituents dictated by the low reactivity of the sugar hydroxyls under the synthetic conditions disclosed. It is apparent that this technology displays significant disadvantages to the present invention; the efficiencies of conversion, the range of potential substituents, the various inversion chemistries that introduce both alternate oxy and amino stereochemical orientations, and the versatile alkylative chemistries of the present invention represent significant improvements over the methods of Kunz's application. Particularly, the present invention provides stereoisomers of monosaccharides that have a nitrogen or a carbon atom attached to the ring in positions 3,4,5 and 6 of a monosaccharide or tetrahydrofurano/pyrano ring system. Of particular interest to the medicinal chemist are the inclusion of linking functionalitites that are going to prove to be stable to physiological conditions thus allowing the drug to reach the desired target intact, or in an active form.

To be practically employed in an effective strategy for drug discovery, carbohydrate blocks need to be simple yet versatile, preferably they should to be amenable to solid-phase synthetic protocols. One of the greatest challenges to be faced by the medicinal chemist in employing carbohydrate blocks for drug design, is in adapting known solution phase carbohydrate chemistries to equivalent solid phase procedures. Due to the specialised nature of carbohydrate chemistry, an entire specific platform of chemistries needs to be developed to ensure that suitable procedures for solid-phase synthesis are at hand. The present invention allows rapid access to the solid phase synthesis of diverse carbohydrate based libraries by the successful implementation of

heretoforth inexecutable chemistry techniques. We have discovered methods that allow introduction of stable linkages – such as C-C bonds, ether bonds and various amido linkages to various monosaccharide, tetrahydropyran, and tetrahydrofuran scaffolds, that assist in the synthesis of novel structures suitable as potential drug candidates. This highly efficient solid phase-based technology, is augmented by stereocenter inversion chemistries that allow access to a wide variety of monosaccharide stereoisomers.

SUMMARY OF THE INVENTION

In a first aspect, the invention provides monosaccharide compounds of general formula I or general formula II,



I II

In which the monosaccharide ring may be of the pyranose or furanose form of any configuration, and the anomeric centre where present, may be of either the α or β configuration,

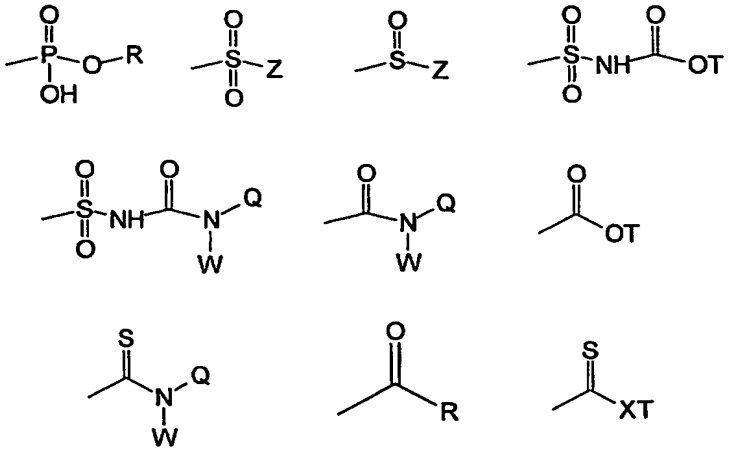
R^1 is X-R,

where X is oxygen, sulphur, sulfoxide (SO_2) or sulfone (SO)

and the group R is independently selected from H, alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl of 1 to 20 atoms which is optionally substituted, branched and/or linear. Typical substituents include but are not limited to OH, NO, NO_2, NH_2, N_3, halogen, CF_3, CHF_2, CH_2F, nitrile, alkoxy, aryloxy, amidine, guanidiniums, carboxylic acid, carboxylic acid ester, carboxylic acid amide, aryl, cycloalkyl, heteroalkyl, heteroaryl, aminoalkyl, aminodialkyl, aminotrialkyl, aminoacyl, carbonyl, substituted or unsubstituted imine, sulfate, sulfonamide, phosphate, phosphoramide, hydrazide, hydroxamate, hydroxamic acid, heteroaryloxy, aminoalkyl, aminoaryl,

aminoheteroaryl, thioalkyl, thioaryl or thioheteroaryl, which may optionally be further substituted,

The groups R^2-R^4 are independently selected from, OR, N(Y)R, R, -(C=O)R, wherein Y is selected from hydrogen, R or the following,



R and X are defined as above for R^1,

T is defined as being independently selected from, alkyl, alkenyl, alkynyl, heteroalkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl of 1 to 20 atoms which is optionally substituted, branched and/or linear. Typical substituents include but are not limited to OH, NO, NO_2, NH_2, N_3, halogen, CF_3, CHF_2, CH_2F, nitrile, alkoxy, aryloxy, amidine, guanidiniums, carboxylic acid, carboxylic acid ester, carboxylic acid amide, aryl, cycloalkyl, heteroalkyl, heteroaryl, aminoalkyl, aminodialkyl, aminotrialkyl, aminoacyl, carbonyl, substituted or unsubstituted imine, sulfate, sulfonamide, phosphate, phosphoramide, hydrazide, hydroxamate, hydroxamic acid, heteroaryloxy, aminoalkyl, aminoaryl, aminoheteroaryl, thioalkyl, thioaryl or thioheteroaryl, which may optionally be further substituted

Z is defined as being independently selected from OH, OM^+ (where M^+ is a cation), or alkyl, alkenyl, alkynyl, heteroalkyl, aminoalkyl, aminoaryl, aryloxy, alkoxy, heteroaryloxy, aminoaryl, aminoheteroaryl, aryl, heteroaryl, arylalkyl or heteroarylalkyl of 1 to 20 atoms which are optionally substituted, branched

and/or linear. Typical substituents include but are not limited to OH, NO, NO_2, NH_2, N_3, halogen, CF_3, CHF_2, CH_2F, nitrile, alkoxy, aryloxy, amidine, guanidiniums, carboxylic acid, carboxylic acid ester, carboxylic acid amide, aryl, cycloalkyl, heteroalkyl, heteroaryl, aminoalkyl, aminodialkyl, aminotrialkyl, aminoacyl, carbonyl, substituted or unsubstituted imine, sulfate, sulfonamide, phosphate, phosphoramide, hydrazide, hydroxamate, hydroxamic acid;, heteroaryloxy, aminoalkyl, aminoaryl, aminoheteroaryl, thioalkyl, thioaryl or thioheteroaryl, which may optionally be further substituted,

And the groups Q and W are independently selected from group R as is defined in the first aspect.

R^5 is defined as H, methyl, $-CH_2OR$, $-CH_2-N(Y)R$, C(O)-N(Y)R, -C(O)OR, or CR wherein R and N(Y)R are defined as above. Separately, the groups Y and R and the groups Q and W when substituted on nitrogen may be combined to form a monocyclic or bicyclic ring structure of 4 to 10 atoms. This ring structure may be further substituted.

In one embodiment of the first aspect, the invention provides monosaccharide compounds of general formula I or general formula II, wherein R^1 and R^2 are defined as in the first aspect, and at least one of R^3 to R^5 contains the group N(Y)R.

Preferrably the compounds of this embodiment are of general formula I, wherein R^1 is defined as in the first aspect, R^2 contains the group OR and at least one of R^3 to R^5 contains the group N(Y)R;

A further preferred embodiment of the first aspect of the invention, provides monosaccharide compounds of general formula I, wherein R^1 is defined as in the first aspect, R^2 contains the group N(Y)R and at least one of R^3 to R^5 contains the group N(Y)R;

In a second embodiment of the first aspect the invention provides monosaccharide compounds of general formula I or general formula II, wherein R^1 and R^2 are defined as in the first aspect, and at least one of R^3 to R^5 contains the group R or –(C=O)R directly attached to the scaffold ring.

In a third embodiment of the first aspect the invention provides monosaccharide compounds of general formula I or general formula II, wherein

R^1 is defined as in the first aspect, R^2 contains the group N(Y)Z and R^3 to R^5 are different and are independently selected from OR.

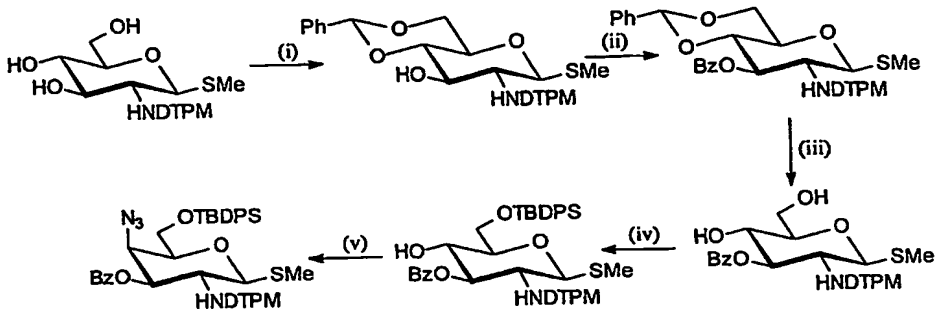
In a second aspect the invention provides for methods for the solution and solid phase synthesis of compounds of general formula I and general formula II according to the first aspect of the invention.

In a third aspect the invention provides monosaccharide compounds of general formula I or general formula II, wherein at least two of R^1-R^5 are not temporarily protected alcohols, thiols or amines. Protecting groups commonly used in the art may be found in T. W. Green and P. G. M. Wuts, *Protecting Groups in Organic Synthesis*, 3rd Edition, Wiley & Sons, Inc., 1999, additionally at least two of R^1-R^5 comprises a chemical functional group which imparts the compound of interest the ability to interact with biological receptor in a pharmaceutically relevant manner.

In a fourth aspect the invention provides for the use of a universal building block as described in PCT/AU00/00025 for the synthesis of compounds of the first aspect including the step of selectively deprotecting a protected hydroxyl, amino or carboxyl group and reacting said functional group with a bioisosteric reagent.

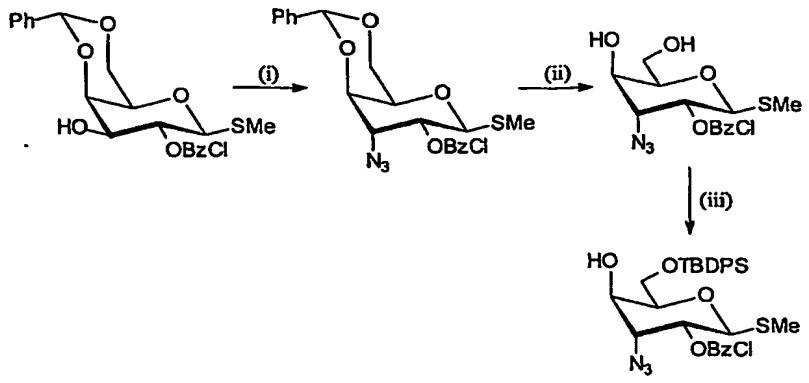
It is understood that the rules of molecular stoichiometry will be upheld by the default addition of hydrogens atoms as required.

Example 1: Synthesis of a Di- *N*-substituted Galactopyranoside Building Block



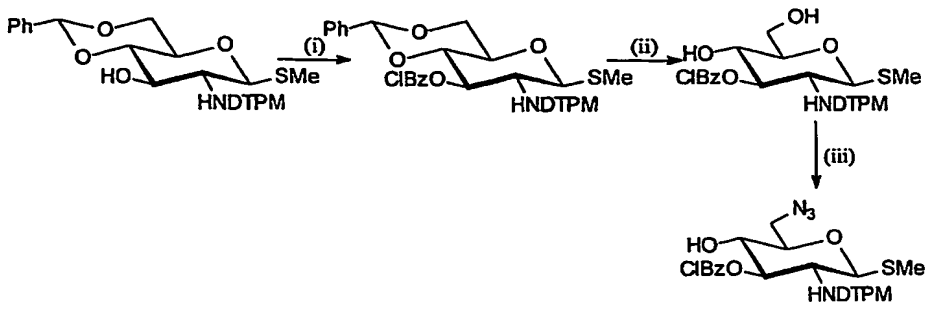
Conditions: (i) α,α-dimethoxytoluene (α,α-DMT), *p*-toluenesulphonic acid (TsOH), acetonitrile (MeCN), 65^{0}C; (ii) Benzoylchloride (BzCl), *N,N*-dimethylaminopyridine (DMAP), 1,2-dichloroethane (1,2-DCE); (iii) methanol (MeOH)/MeCN/water, TsOH; (iv) *t*-butyldiphenylsilylchloride (TBDPS-Cl), imidazole, 1,2-DCE; (v) Tf_2O, pyridine, DCM, -20^{0}C, (b) NaN_3, DMF, 1hr, RT.

Example 2: Synthesis of a Gulopyranoside Building Block



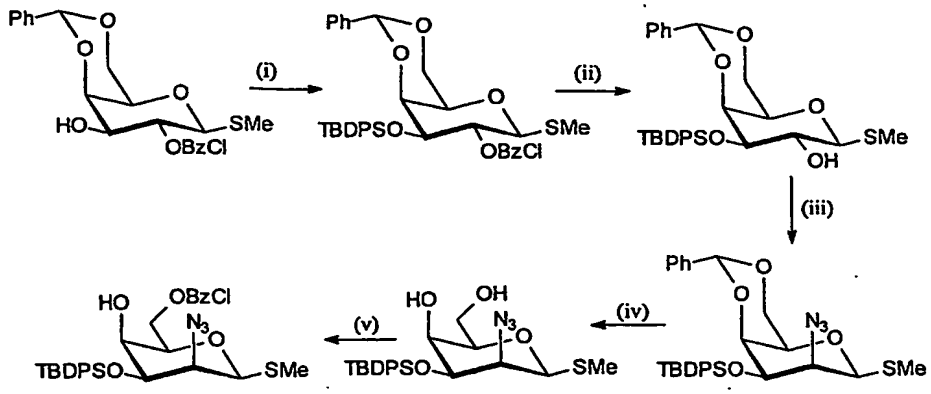
Conditions: (i) (a) trifluoromethanesulfonic anhydride (Tf_2O), pyridine, -20°C, dichloromethane (DCM), 1 hour, (b) sodium azide (NaN_3), *N,N*-dimethylformamide (DMF), 50°C, 5 hours, quantitative; (ii) TsOH, MeCN/ MeOH/water (12:3:1), 90°C, 6 hours, (iii) TBDPSCl, DMAP, pyridine, 120°C, 12 hours, 88% (over 2 steps).

Example 3: Synthesis of a Glucopyranoside Building BLock



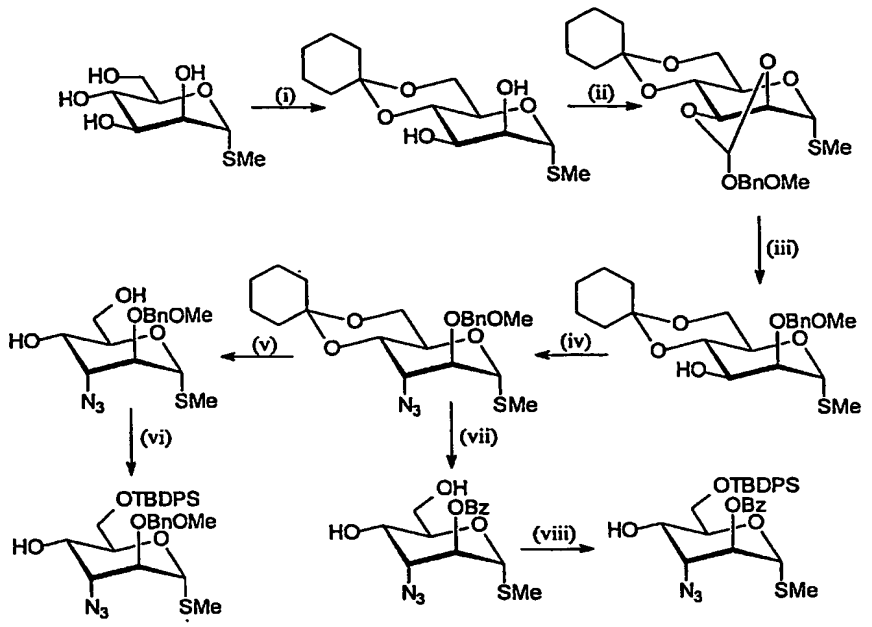
Conditions: (i) chlorobenzoylchloride (ClBzCl), DMAP, 1,2-DCE; (ii) TsOH, MeCN/MeOH/water, (iii) (a) Tf_2O, pyridine, -20°C, DCM, 1 hour, (b) NaN_3, DMF, 50°C, 5 hours.

Example 4: Synthesis of a Tallopyranoside Building Block



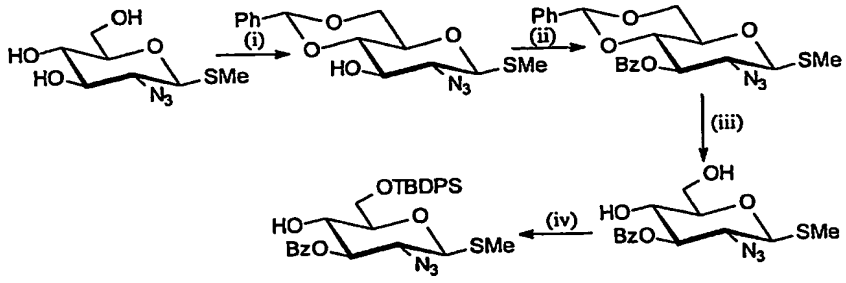
Conditions: (a) TBDPSCl, imidazole, 1,2-DCE, reflux; (ii) NaOMe/MeOH; (iii) (a) Tf_2O, pyridine, -20^{0}C, DCM, 1 hour, (b) NaN_3, DMF, 50^{0}C, 5 hours; (iv) TsOH, MeCN/MeOH/water; (v) chlorobenzoylchloride, DMAP, 1,2-DCE.

Example 5: Synthesis of a Mannopyranoside Building Block



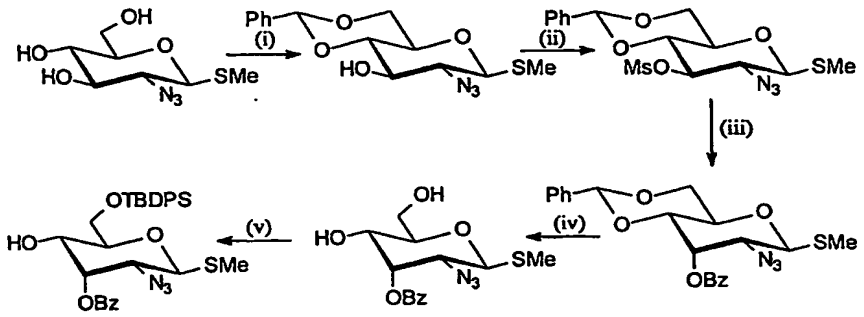
Conditions: (i) cyclohexanone dimethylacetal, TsOH, MeCN; (ii) *p*-methoxybenzaldehyde · dimethylacetal, TsOH, MeCN; (iii) DIBAL, -78°C, diethylether; (iv) (a) Tf_2O, pyridine, -20°C, DCM, 1 hour, (b) NaN_3, DMF, 50°C, 5 hours; (v) TsOH, MeCN/MeOH/water; (vi) TBDPSCl, DMAP, 1,2-DCE; (vii) (a) CAN, (b) BzCl, DMAP, 1,2-DCE, (c) TsOH, MeCN/MeOH/water; (viii) TBDPSCl, DMAP, 1,2-DCE.

Example 6: Synthesis of a Glucopyranoside Building Block



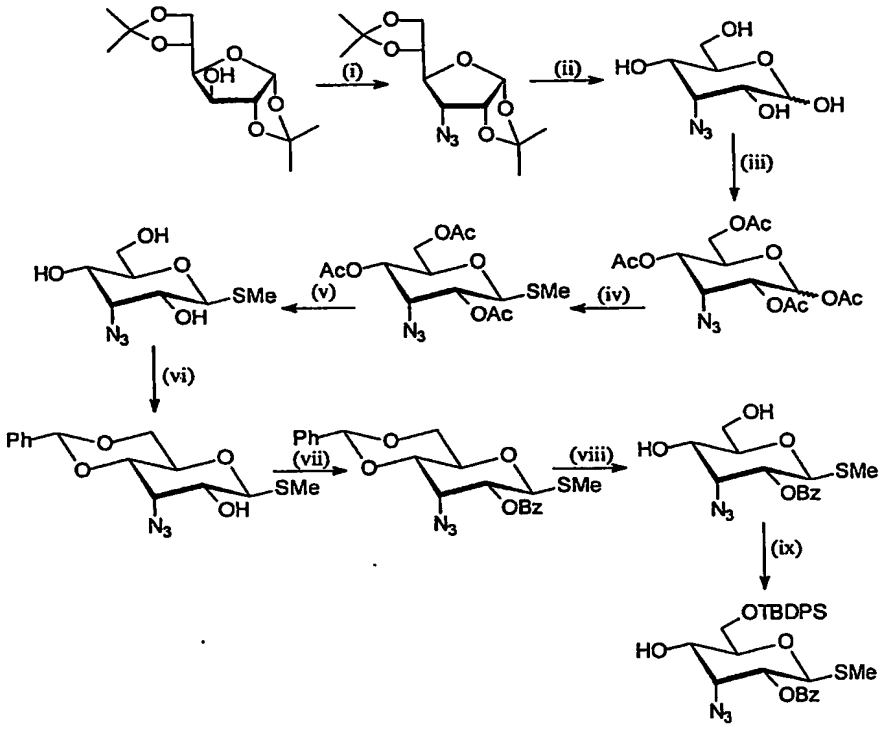
Conditions: (i) α,α-DMT, TsOH, MeCN; (ii) 1,2-DCE, BzCl, DMAP; (iii) TsOH, MeOH/MeCN; (iv) TBDPS-Cl, DMAP, 1,2-DCE.

Example 7: Synthesis of a Allopyranoside Building Block



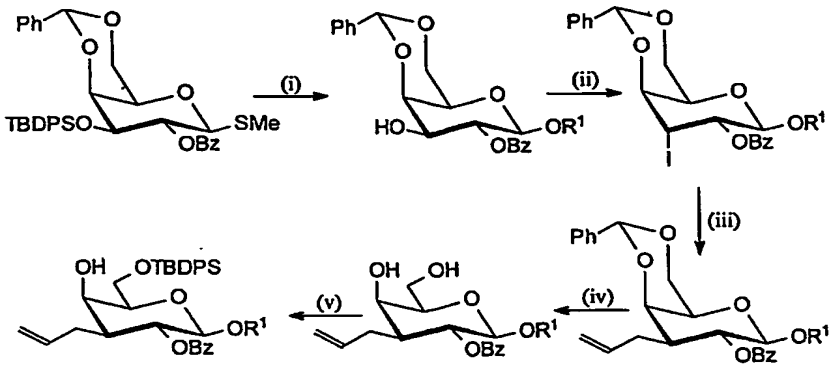
Conditions: (i) α,α-DMT, TsOH, MeCN; (ii) DCM/pyridine, MsCl, DMAP, O^0C; (iii) sodium benzoate, dimethylsulphoxide (DMSO), 140^0C; (iv) TsOH, MeOH/MeCN/water; (v) TBDPS-Cl, imidazole, DCM, 1 hour, reflux.

Example 8: Synthesis of a Galactopyranoside 3-Deoxy 3-Alkyl Building Block



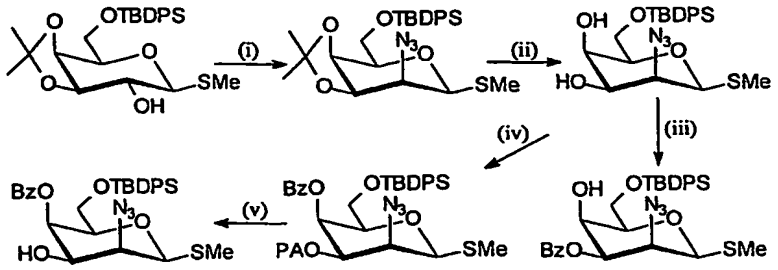
Conditions: (i) Tf_2O, pyridine, DCM; (b) NaN_3, DMF; (ii) acetone, H^+; (iii) Ac_2O, pyridine; (iv) hexamethyldisilazane, I_2, CH_3-S-S-CH_3; (v) NaOMe/MeOH; (vi) TsOH, α,α-dimethoxytoluene, MeCN; (vii) benzoylchloride, 1,2-DCE, pyridine, DMAP; (viii) TsOH, MeOH, H_2O, MeCN; (ix) TBDPS-Cl, imidazole, 1,2-DCE.

Example 9: Synthesis of a Galactopyranoside 3-Deoxy 3-Alkyl Building Block.



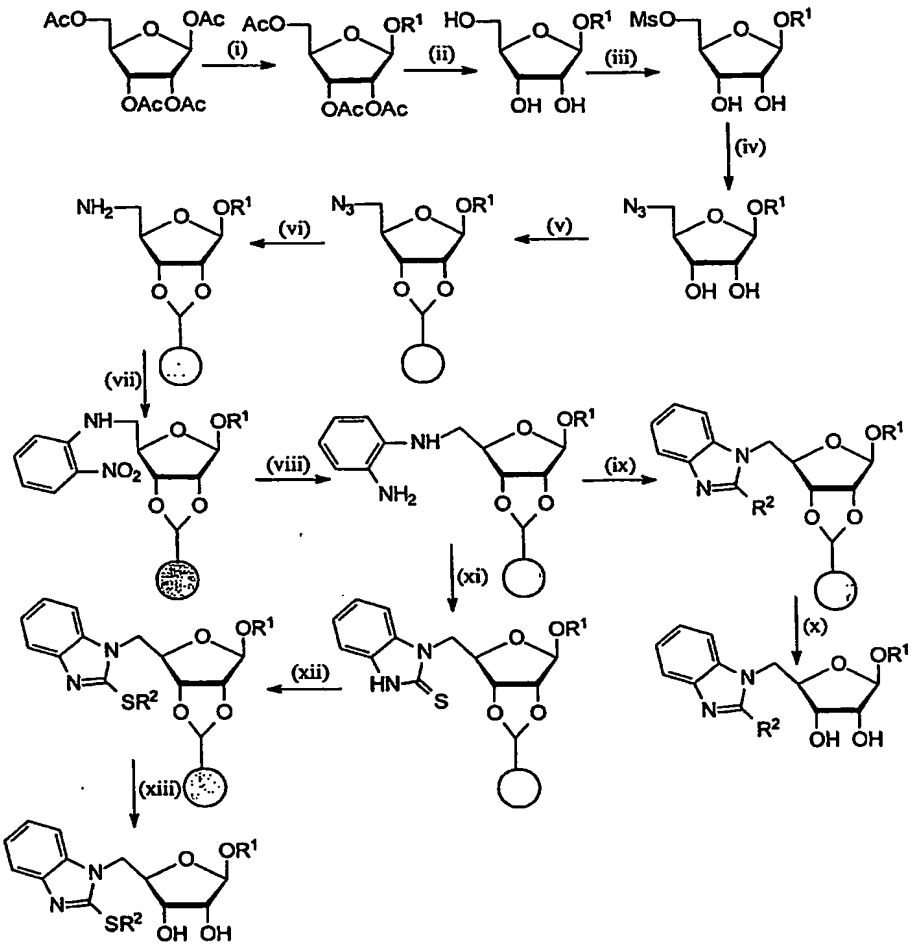
Conditions: (i) (a) DMTST, DCM, Mol. Sieves, R^1-OH; (b) TBAF/THF; (ii) $(Ph)_3P$, I_2, Imidazole; (iii) tintributylallane, AIBN, Toluene, reflux; (iv) MeCN/MeOH/water, TsOH; (v) TBDPS-Cl, DMAP, 1,2-DCE.

Example 10: Further Syntheses of Tallopyranoside Building Blocks



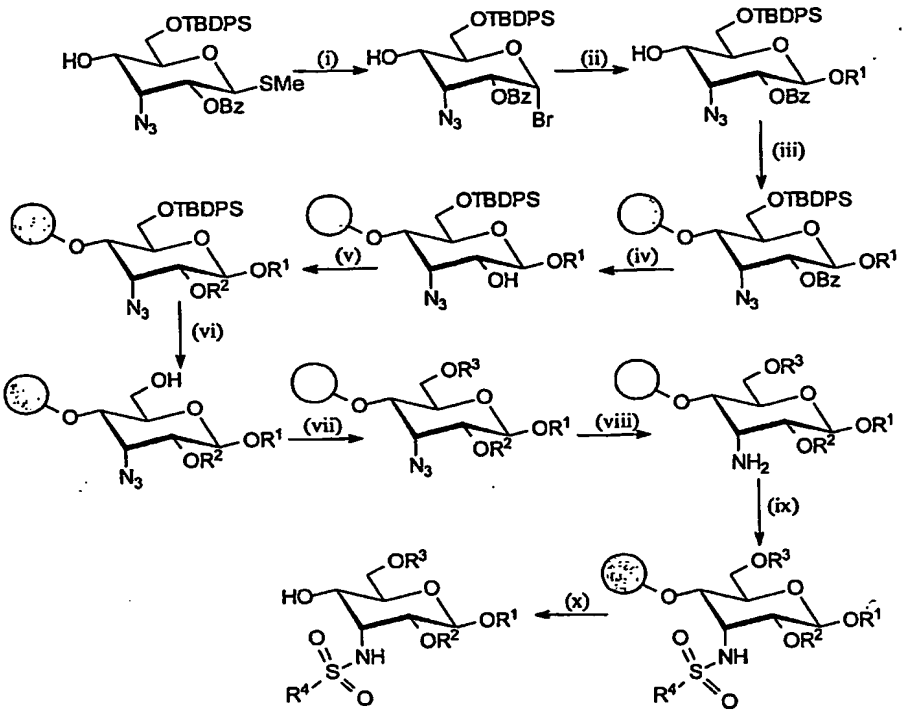
Conditions: (i) (a) Tf_2O/Py, (b) NaN_3, DMF; (ii) TsOH, MeOH/MeCN/water; (iii) BzCl, DMAP, 1,2-DCE; (iv) (a) phenoxyacetyl-Cl (PACl)/pyridine; (b) Bz_2O/pyridine; (v) $MeNH_2$/THF.

Example 11: Synthesis of a Ribofuranoside Building Block and Library



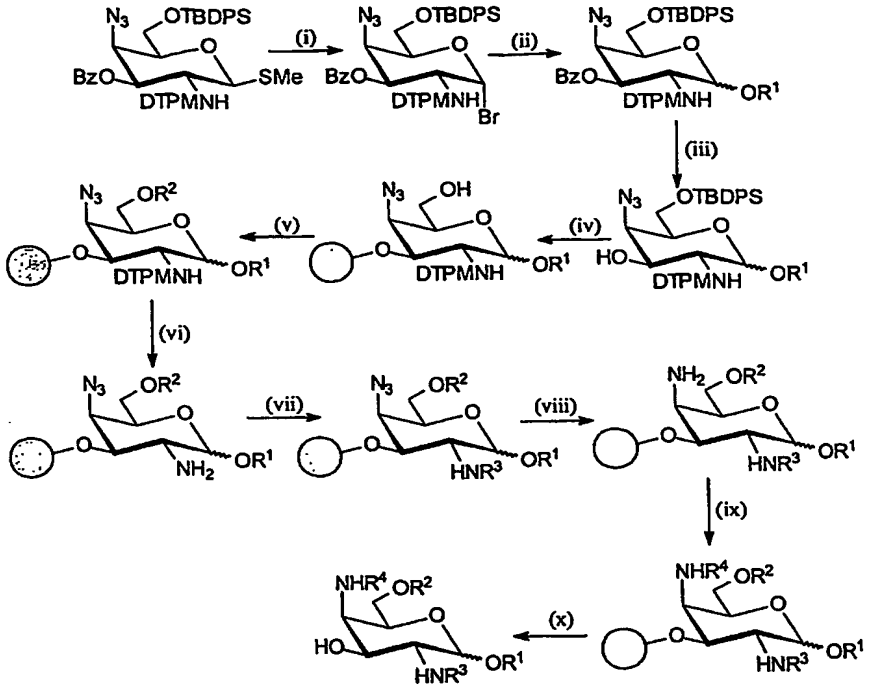
Conditions: (i) TMSOTf, HOR^1, DCM, Mol. Sieves; (ii) NaOMe/MeOH; (iii) MsCl, pyridine, DCM; (iv) NaN_3, DMF; (v) methyl ethanoyl-2-oxy-*p*-benzaldehyde, DMF, H^+; (vi) (a) KOH, MeOH, (b) HBTU, DIPEA, DMF; (vii) DTT, Base; (viii) *m*-fluoro-nitrobenzene, diisopropylethylamine (DIPEA), DMF; (ix) $Na_2S_2O_4$, viologen, K_2CO_3, DCM/H_2O; (x) R^2CHO, (*N*-methylpyrollidinone) NMP (xi) 10% TFA/ DCM/MeOH (9:1); (xii) thiocarbonyldiimidazole, THF; (xiii) R^2-X, DIPEA, DMF (xiv) 10% TFA/(DCM/MeOH (9:1)).

Example 12: Solid Phase Synthesis of a Library Based on Building Block x



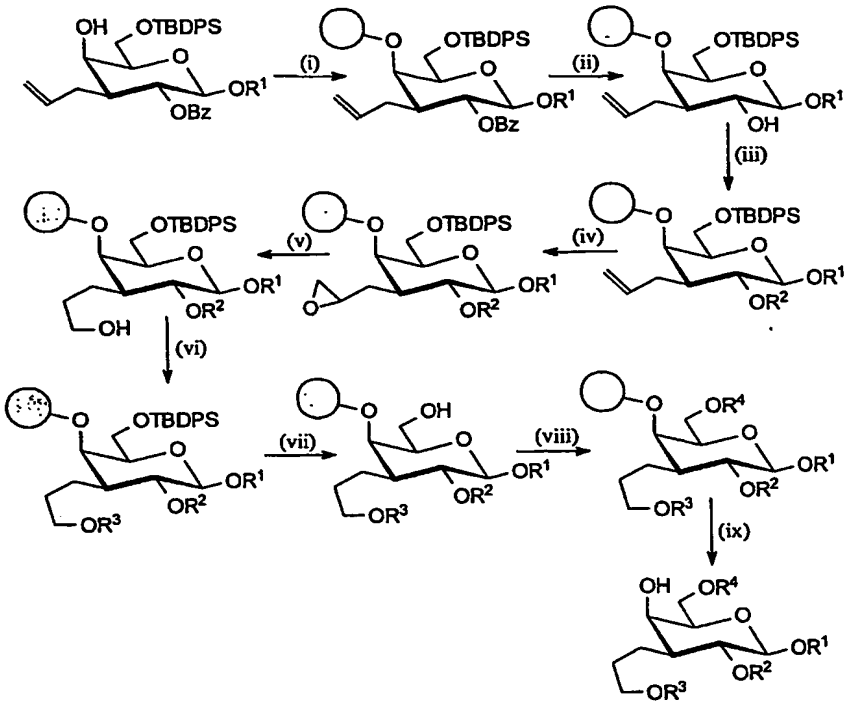
Conditions: (i) Br_2; (ii) AgOTf, R^1OH, DCM, Mol. Sieves; (iii) $BF_3.OEt_2$, DCM; (iv) NaOMe/MeOH/THF; (v) R^2-X, Base, DMF; (vi) TBAF/THF; (vii) R^3-X, Base, DMF; (viii) DTT, Base; (ix) (a) R^4-sulphonyl chloride (b) H_2N-R^4; (x) TFA.

Example 13: Solid Phase Synthesis of a Library Based on Building Block X2



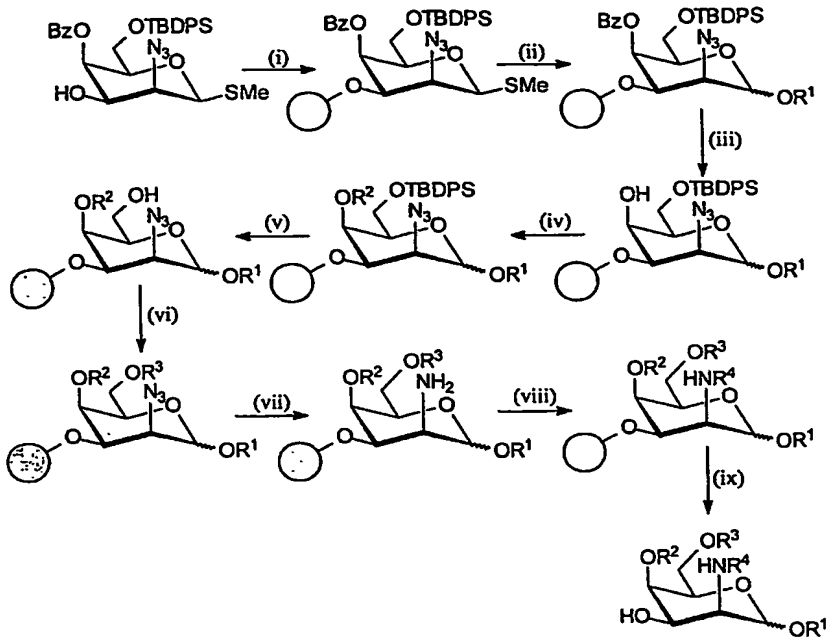
Conditions: (i) Br_2; (ii) R^1-OH, AgOTf, DCM, Mol. Sieves; (iii) NaOMe/MeOH; (iv) $BF_3.OEt_2$, DCM; (v) R^2-X, Base, DMF; (vi) hydrazine hydrate, DMF; (vii) R^3-(isocyanate or isothiocyanate); (viii) DTT, base; (ix) R^4-acylchloride; (x) TFA

Example 14: Solid Phase Synthesis of a Library Based on Building Block X3



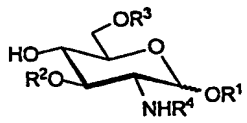
Conditions: (i) $BF_3.OEt_2$; (ii) NaOMe/MeOH; (iii) R^2-X, Base, DMF, (iv) MCPBA, DCM; (v) $NaCNBH_3$, $BF_3.OEt_3$, THF; (vi) R^3-X, Base, DMF; (vii) TBAF/THF; (viii) R^4-X, Base, DMF; (ix) TFA.

Exanple 15: Synthesis of a Library Based on Building Block (t)



Conditions: (i) $BF_3.OEt_2$, DCM; (ii) DMTST, DCM, R^1-OH; (iii) NaOMe/MeOH; (iv) R^2-X, base, DMF; (v) TBAF/THF; (vi) R^3-X, base, DMF; (vii) DTT, base; (viii) R^4-chloroformate, DIPEA, DCM; (ix) TFA.

Compounds synthesised with Building Block **A1**



A1

Compound No.	R^1	R^2	R^3	R^4
	Me	4-Br-Bn	Glycolate	β-Alanine
	Me	4-Br-Bn	Glycolate	3-NH_2-Bz
	Me	4-Br-Bn	4-CO_2H-Bn	β-Alanine
	Me	4-Br-Bn	4-CO_2H-Bn	3-NH_2-Bz
	Me	4-Br-Bn	3-NH_2-Bn	Glycolate
	Me	4-Br-Bn	3-NH_2-Bn	4-CO_2H-Bz
	Me	Glycolate	Bn	β-Alanine
	Me	Glycolate	Bn	3-NH_2-Bz
	Me	Glycolate	4-Br-Bn	β-Alanine
	Me	Glycolate	4-Br-Bn	3-NH_2-Bz
	Me	Glycolate	3-NH_2-Bn	Bz
	Me	Glycolate	3-NH_2-Bn	4-Cl-Bz
	Me	4-CO_2H-Bn	Bn	β-Alanine
	Me	4-CO_2H-Bn	Bn	3-NH_2-Bz
	Me	4-CO_2H-Bn	4-Br-Bn	β-Alanine
	Me	4-CO_2H-Bn	4-Br-Bn	3-NH_2-Bz
	Me	4-CO_2H-Bn	3-NH_2-Bn	Bz
	Me	4-CO_2H-Bn	3-NH_2-Bn	4-Cl-Bz
	Me	3-NH_2-Bn	Bn	Glycolate
	Me	3-NH_2-Bn	Bn	4-CO_2H-Bz
	Me	3-NH_2-Bn	4-Br-Bn	Glycolate
	Me	3-NH_2-Bn	4-Br-Bn	4-CO_2H-Bz
	Me	3-NH_2-Bn	Glycolate	Bz
	Me	3-NH_2-Bn	Glycolate	4-Cl-Bz
	Me	3-NH_2-Bn	4-CO_2H-Bn	Bz
	Me	3-NH_2-Bn	4-CO_2H-Bn	4-Cl-Bz
	Et	Bn	Glycolate	β-Alanine

	Et	Bn	Glycolate	3-NH_2-Bz
	Et	Bn	4-CO_2H-Bn	β-Alanine
	Et	Bn	4-CO_2H-Bn	3-NH_2-Bz
	Et	Bn	3-NH_2-Bn	Glycolate
	Et	Bn	3-NH_2-Bn	4-CO_2H-Bz
	Et	4-Br-Bn	Glycolate	β-Alanine
	Et	4-Br-Bn	Glycolate	3-NH_2-Bz
	Et	4-Br-Bn	4-CO_2H-Bn	β-Alanine
	Et	4-Br-Bn	4-CO_2H-Bn	3-NH_2-Bz
	Et	4-Br-Bn	3-NH_2-Bn	Glycolate
	Et	4-Br-Bn	3-NH_2-Bn	4-CO_2H-Bz
	Et	Glycolate	Bn	β-Alanine
	Et	Glycolate	Bn	3-NH_2-Bz
	Et	Glycolate	4-Br-Bn	β-Alanine
	Et	Glycolate	4-Br-Bn	3-NH_2-Bz
	Et	Glycolate	3-NH_2-Bn	Bz
	Et	Glycolate	3-NH_2-Bn	4-Cl-Bz
	Et	4-CO_2H-Bn	Bn	β-Alanine
	Et	4-CO_2H-Bn	Bn	3-NH_2-Bz
	Et	4-CO_2H-Bn	4-Br-Bn	β-Alanine
	Et	4-CO_2H-Bn	4-Br-Bn	3-NH_2-Bz
	Et	4-CO_2H-Bn	3-NH_2-Bn	Bz
	Et	4-CO_2H-Bn	3-NH_2-Bn	4-Cl-Bz
	Et	3-NH_2-Bn	Bn	Glycolate
	Et	3-NH_2-Bn	Bn	4-CO_2H-Bz
	Et	3-NH_2-Bn	4-Br-Bn	Glycolate
	Et	3-NH_2-Bn	4-Br-Bn	4-CO_2H-Bz
	Et	3-NH_2-Bn	3-NH_2-Bn	Bz
	Et	3-NH_2-Bn	3-NH_2-Bn	4-Cl-Bz
	Et	3-NH_2-Bn	4-CO_2H-Bn	Bz
	Et	3-NH_2-Bn	4-CO_2H-Bn	4-Cl-Bz
	Et	Et	Glycolate	β-Alanine
	Et	Et	Glycolate	3-NH_2-Bz
	Et	Et	4-CO_2H-Bn	β-Alanine
	Et	Et	4-CO_2H-Bn	3-NH_2-Bz
	Et	Et	3-NH_2-Bn	Glycolate
	Et	Et	3-NH_2-Bn	4-CO_2H-Bz

	Et	Glycolate	Me	β-Alanine
	Bn	Glycolate	Me	3-NH_2-Bz
	Bn	Glycolate	Et	β-Alanine
	Bn	Glycolate	Et	3-NH_2-Bz
	Bn	Glycolate	3-NH_2-Bn	Me
	Bn	Glycolate	3-NH_2-Bn	$C_2H_5C(O)$
	Bn	4-CO_2H-Bn	Me	β-Alanine
	Bn	4-CO_2H-Bn	Me	3-NH_2-Bz
	Bn	4-CO_2H-Bn	Et	β-Alanine
	Bn	4-CO_2H-Bn	Et	3-NH_2-Bz
	Bn	4-CO_2H-Bn	3-NH_2-Bn	Me
	Bn	4-CO_2H-Bn	3-NH_2-Bn	$C_2H_5C(O)$
	Bn	3-NH_2-Bn	Me	Glycolate
	Bn	3-NH_2-Bn	Me	4-CO_2H-Bz
	Bn	3-NH_2-Bn	Et	Glycolate
	Bn	3-NH_2-Bn	Et	4-CO_2H-Bz
	Bn	3-NH_2-Bn	3-NH_2-Bn	Me
	Bn	3-NH_2-Bn	3-NH_2-Bn	$C_2H_5C(O)$
	Bn	3-NH_2-Bn	4-CO_2H-Bn	Me
	Bn	3-NH_2-Bn	4-CO_2H-Bn	$C_2H_5C(O)$

Compounds Synthesised with Building Block A2

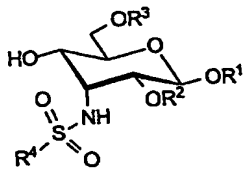
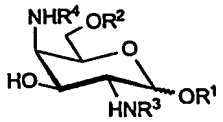


Table 2

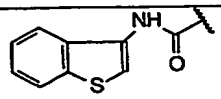
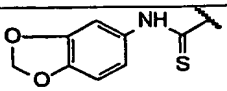
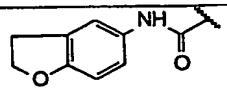
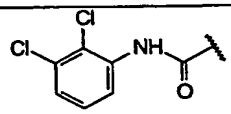
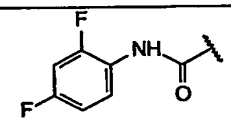
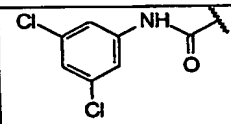
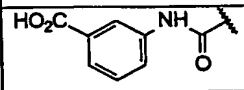
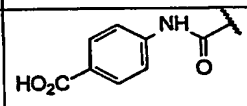
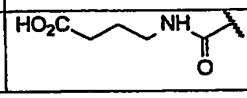
Comp. No.	R^1	R^2	R^3	R^4
	Isopropyl	Glycolate	Lys mimetic 1	toluyl
	Isopropyl	4-CO_2H-Bn	Lys mimetic 2	4-F-Phenyl
	Isopropyl	3-CO_2H-Bn	Lys mimetic 3	phenyl
	Naphthyl	Lys mimetic 1	Phe mimetic 1	3-chlorophenyl
	Naphthyl	Lys mimetic 2	Phe mimetic 2	methyl
	Naphthyl	Lys mimetic 3	Phe mimetic 3	hydroxyl
	Biphenyl	Phe mimetic 1	Trp mimetic 1	3-chlorophenyl
	Biphenyl	Phe mimetic 2	Trp mimetic 2	methyl
	Biphenyl	Phe mimetic 3	Trp mimetic 3	hydroxyl
	Benzyl	Trp mimetic 1	Glycolate	biphenylmethyl
	Benzyl	Trp mimetic 2	4-CO_2H-Bn	3,4-dichlorophenyl
	Benzyl	Trp mimetic 3	3-CO_2H-Bn	4-chlorophenyl

Compounds Synthesised with Building Block A3

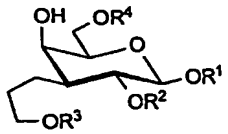


A3

Table 3

Comp. No.	R^1	R^2	R^3	R^4
	Isopropyl	Glycolate		Lys mimetic 1 (*N*-linked acyl)
	Isopropyl	4-CO_2H-Bn		Lys mimetic 2 (*N*-linked acyl)
	Isopropyl	3-CO_2H-Bn		Lys mimetic 3 (*N*-linked acyl)
	Naphthyl	Lys mimetic 1 (*O*-linked)		Phe mimetic 1 (*N*-linked acyl)
	Naphthyl	Lys mimetic 2 (*O*-linked)		Phe mimetic 2 (*N*-linked acyl)
	Naphthyl	Lys mimetic 3 (*O*-linked)		Phe mimetic 3 (*N*-linked acyl)
	Biphenyl	Phe mimetic 1 (*O*-linked)		Lys mimetic 1 (*N*-linked acyl)
	Biphenyl	Phe mimetic 2 (*O*-linked)		Lys mimetic 2 (*N*-linked acyl)
	Biphenyl	Phe mimetic 3 (*O*-linked)		Lys mimetic 3 (*N*-linked acyl)

Compounds Synthesised with Building Block A4



5

Table 4

Comp. No.	R^1	R^2	R^3	R^4
	4-chlorobenzyl	Phe mimetic 1 (O-linked ether)	Glycolate	Lys mimetic 1 (O-linked ether)
	4-chlorobenzyl	Phe mimetic 2 (O-linked ether)	4-HO_2C-benzyl	Lys mimetic 2 (O-linked ether)
	4-chlorobenzyl	Phe mimetic 3 (O-linked ether)	3-HO_2C-benzyl	Lys mimetic 3 (O-linked ether)
	Isopropyl	Lys mimetic 1 (O-linked ether)	Phe mimetic 1 (O-linked ether)	Trp mimetic 1 (O-linked ether)
	Isopropyl	Lys mimetic 2 (O-linked ether)	Phe mimetic 2 (O-linked ether)	Trp mimetic 2 (O-linked ether)
	Isopropyl	Lys mimetic 3 (O-linked ether)	Phe mimetic 3 (O-linked ether)	Trp mimetic 3 (O-linked ether)
	Naphthyl	Phe mimetic 1 (O-linked ether)	Glycolate	Lys mimetic 1 (O-linked ether)
	Naphthyl	Phe mimetic 2 (O-linked ether)	4-HO_2C-benzyl	Lys mimetic 2 (O-linked ether)
	Naphthyl	Phe mimetic 3 (O-linked ether)	3-HO_2C-benzyl	Lys mimetic 3 (O-linked ether)
	Glycolate	Phe mimetic 1 (O-linked ether)	Lys mimetic 1 (O-linked ether)	Trp mimetic 1 (O-linked ether)
	4-HO_2C-benzyl	Phe mimetic 2 (O-linked ether)	Lys mimetic 2 (O-linked ether)	Trp mimetic 2 (O-linked ether)
	3-HO_2C-benzyl	Phe mimetic 3 (O-linked ether)	Lys mimetic 3 (O-linked ether)	Trp mimetic 3 (O-linked ether)

Compounds Synthesised with Building Block A5

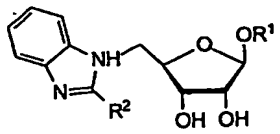
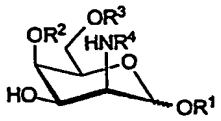


Table 4

Comp. No.	R^1	R^2
	Methyl	4-chlorophenyl
	Methyl	biphenyl
	Methyl	octyl
	Isopropyl	4-chlorophenyl
	Isopropyl	biphenyl
	Isopropyl	octyl
	Benzyl	4-chlorophenyl
	Benzyl	4-nitrophenyl
	Benzyl	octyl
	Naphthyl	4-chlorophenyl
	Naphthyl	4-nitrophenyl
	Naphthyl	octyl

Compounds Synthesised with Building Block A6

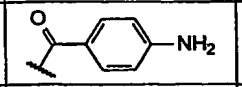
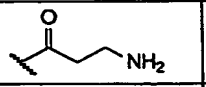
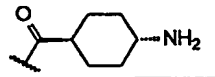
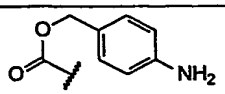
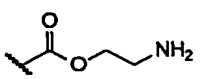
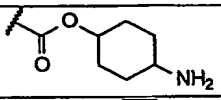
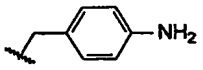
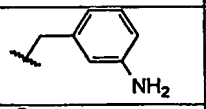
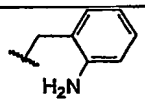
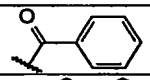
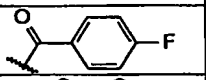
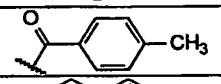
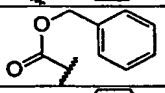
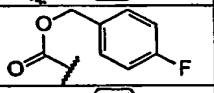
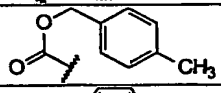
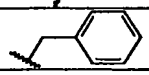
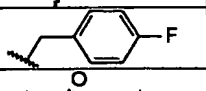
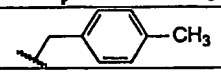
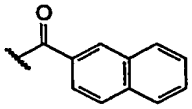
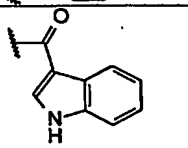
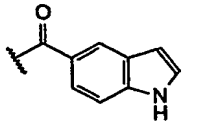
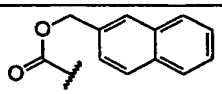
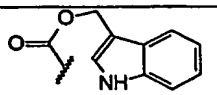
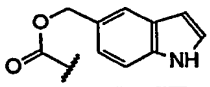
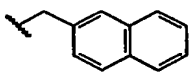
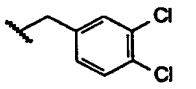
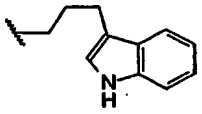


5

Table 5

	R^1	R^2	R^3	R^4
	Benzyl	Trp mimetic 1 (*O*-linked ether)	Glycolate	Lys mimetic 1 (*N*-linked carbamate)
	Benzyl	Trp mimetic 2 (*O*-linked ether)	4-CO_2H-Bn	Lys mimetic 2 (*N*-linked carbamate)
	Benzyl	Trp mimetic 3 (*O*-linked ether)	3-CO_2H-Bn	Lys mimetic 3 (*N*-linked carbamate)
	Isopropyl	Glycolate	Lys mimetic 1 (*O*-linked ether)	Phe mimetic 1 (*N*-linked carbamate)
	Isopropyl	4-CO_2H-Bn	Lys mimetic 2 (*O*-linked ether)	Phe mimetic 2 (*N*-linked carbamate)
	Isopropyl	3-CO_2H-Bn	Lys mimetic 3 (*O*-linked ether)	Phe mimetic 3 (*N*-linked carbamate)
	Naphthyl	Glycolate	Phe mimetic 1 (*O*-linked ether)	Lys mimetic 1 (*N*-linked carbamate)
	Naphthyl	4-CO_2H-Bn	Phe mimetic 2 (*O*-linked ether)	Lys mimetic 2 (*N*-linked carbamate)
	Naphthyl	3-CO_2H-Bn	Phe mimetic 3 (*O*-linked ether)	Lys mimetic 3 (*N*-linked carbamate)
	Biphenyl	Lys mimetic 1 (*O*-linked ether)	Glycolate	Phe mimetic 1 (*N*-linked carbamate)
	Bphenyl	Lys mimetic 2 (*O*-linked wther)	4-CO_2H-Bn	Phe mimetic 2 (*N*-linked carbamate)
	Biphenyl	Lys mimetic 3 (*O*-linked ether)	3-CO_2H-Bn	Phe mimetic 3 (*N*-linked carbamate)

[§]The various scaffold substituents Lys, Phe, and Trp mimetics 1,2 and 3, are listed in **Table 3** below. It is noted that in some case amine protection is required, which is typically effected by Boc protection. It is further noted that in some cases an O-linked mimetic is required and in other cases an *N*-linked mimetic is required. In the cases of the O-linked Lys mimetics, the mimetic is coupled as either the para, ortho or meta nitrobenzyl derivative and subsequently reduced to the amine. All carboxyl groups are typically protected as methyl esters during coupling and cleaved with basic media.

	Mimetic 1	**Mimetic 2**	**Mimetic 3**
Lys (*N*-linked acyl)			
Lys (*N*-linked carbamate)			
Lys (*O*-linked ether)			
Phe (*N*-linked acyl)			
Phe (*N*-linked carbamate)			
Phe (*O*-linked ether)			
Trp (*N*-linked acyl)			
Trp (*N*-linked carbamate)			
Trp (*O*-linked ether)			

It should be appreciated that various changes and modifications can be made to the embodiments without departing from the spirit and scope of the invention.

Dated this 8th day of August 2002

Alchemia Pty Ltd

By their Patent Attorneys

CULLEN & CO.